such an arrangement. I have modified claims 1, 12 and 23, to more clearly indicate that both the protein and DNA are immobilized during the detection step. The helicase-DNA complex is not immobilized in Giordano. Giordano, et al., however, does provide for a protein to be used in the detection of the nucleic acid. In claim 5 of Giordano, an antibody is coated on a solid support, *then* nucleic acid (resulting from a helicase reaction) is added to the antibody-coated solid support. *Importantly*, in Giordano, the order of addition to the solid support is *reversed* from the current invention. This will not allow the amount of protein bound to the DNA to be determined since a constant amount of protein is bound to the solid support. The amount of DNA bound to the antibody is then detected with a label on the DNA. Giordano is significantly different from the current invention:

a. The instant invention requires DNA to be bound to the solid support (i.e. claim 1, step (a)), followed by addition of a test protein and its detection.
b. The detection step in Giordano is of the DNA, and in the instant invention is the protein.

3. Claims 1-2, 5, 7, 12, 14, 17, and 23 were rejected as being anticipated by Shi et al. (US Pat 5,919,626). The method captures from solution one strand of a specific polynucleotide analyte by hybridization to an immobilized nucleic acid. Shi et al. mention that the invention could be used in protein binding assays on col 5 lines 49 and 64, col 6 line 5, and col 8 line 7. All of their discussion around protein binding assays is broad (e.g. "useful in genetic analysis and other screening applications such as protein-DNA binding assays"). Such binding assays are not described as DNA-structure specific binding protein assays. Shi et al. do not describe the use of specific DNA structures to capture proteins to the solid support. Detection of the Protein-DNA complexes is not discussed at all in Shi et al. The only discussion of proteins is on col 13 wheirein Shi et al. describe the

use of their invention in mediating ligation of DNA onto a solid-support. In this case, the protein DNA complex is clearly not detected on the solid phase, as in the case of the instant invention.

4. Claims 1-2, 9, 12, 14, 20, and 23 were rejected as being anticipated by Peterson et al. (US Pat. 5,563,036). Peterson describes a method to detect transcription factors bound to specific DNA sequences immobilized on a solid support. Such a method requires that the protein bind nucleic acid in a sequence-specific manner. Additionally, this method requires the immobilized DNA contain specific DNA sequences known to bind the transcription factor. Peterson requires specific sequences to be present in the nucleic acid of their invention (claim 1, and col 6 lines 40-50). Such a method will not reveal the binding of a structure-specific binding protein, since the immobilized DNA does not require specific structures for the protein to bind. The current invention does not require specific sequences, but does require a specific structure (claim 1 of the current invention). This is a key difference between Peterson and the present invention. In addition to the sequence requirements, the protein and detection methods will necessarily be different between Peterson and the present invention (see 7 below).
5. *Claim Rejections – 35 USC § 103*
6. I believe the current invention is not obvious for the following reasons.
7. Claims 10-11 and 21-22 are rejected as being unpatentable over Giordano and Peterson, which teach screening assays. Giordano teaches helicase assays, but not assays directly measuring the binding of protein to a DNA structure. As mentioned in (2) above, I have amended the claims to clearly show that detection of the protein-DNA complex is immobilized. Additionally, as discussed in (2) above, the order of addition to the solid support is reversed in Giordano (i.e. the protein is immobilized) which allows detection of the nucleic acid. The significant differences as outlined between the present invention and Giordano show that the choice of DNA-PK or anti-DNA-PK antibodies are not optimizations of the Giordano

protocol. Peterson teaches sequence-specific DNA binding assays, not structure-specific binding assays. Thus, at least three different specific requirements are needed in the present invention compared to Peterson: (1) a DNA substrate with a specific structure, and (2) proteins capable of binding this structure, (3) a detection means for the protein in (2). Selection of a different antibody in the present invention will not allow detection of a relevant complex in the method of Peterson, since a specific DNA structure is not used. Additionally, a protein that binds a specific DNA structure is not contemplated in Peterson. Furthermore, DNA-PK does not bind DNA in a sequence-specific manner [Smider and Chu, (1997) Semin.Immunol. pp.189-97], so this choice of protein/detection method is not an optimization of the protocol taught in Peterson.

8. Claims 4, 6, 16, and 18 are rejected as being unpatentable over Giordano, Shi, or Peterson in view of Yamane. I believe it is not obvious to use the methods of Giordano, Shi, or Peterson in view of using damaged DNA in the method of Yamane. Yamane teaches the use of UV irradiated DNA to achieve immobilization of the DNA. As mentioned in (7) above, the method of Giordano is significantly different from the present invention due to the indirect nature of protein detection, as well as the order in which analytes are added to the solid support. Further, as the examiner notes, Peterson requires that sequence specific binding occur in their method. If damaged DNA is used concomitantly with sequence specific DNA and a sequence specific binding protein, anomalous results are likely to occur. The present invention uses DNA comprising a specific structure (not sequence) as well as structure specific binding proteins, and specific detection of these proteins. *These are several independent requirements which are not obvious design choices from Shi, Yamane, or Peterson.* For example, using a UV-irradiated DNA as described by Yamane in the invention by Peterson, would additionally require departure from the sequence specific requirement by Peterson, *as well as* different proteins

(e.g. DNA repair proteins) *as well as* different detection means specific for these proteins.

9. I appreciate the consideration of my arguments to overcome the previous 102 references.
10. As stated above, the current claim amendment should embody the current invention in regards to direct detection of the protein-DNA complex on the solid support, and hope the examiner agrees that such arguments stated herein overcome the Giordano reference.
11. As examiner notes, Shi et al. contemplates the use of immobilized oligonucleotides to bind proteins. However, (see 3 above) Shi does not contemplate utilizing specific DNA structures to bind structure-specific DNA binding proteins (like DNA repair proteins). Methods to detect binding are not disclosed in Shi et al. Thus, Shi provides a method for immobilizing DNA to a solid support, which might be useful in claim 1 (a) if the DNA were modified to contain a specific structure of the present invention, but do not contemplate the importance or techniques required to detect structure-specific binding proteins.

Claim Amendments

1. (currently amended) A method for measuring DNA-structure specific binding activity of a test protein comprising the steps of:
   a) Immobilizing a single DNA substrate comprising a specific DNA structure to a solid support, then contacting the DNA substrate with a test protein or mixture of proteins; and
   b) Detecting the protein or mixture of proteins from step (a) while the protein and the DNA substrate ~~is~~ are ~~still~~ bound to the solid support.

2. (original) The method according to claim 1, wherein the solid support is a microtiter plate.

3. (canceled) The method according to claim 1, wherein the immobilized nucleic acid substrate comprises DNA.

4. (previously amended) The method according to claim 1, wherein the DNA is damaged.

5. (original) The method according to claim 1, wherein the nucleic acid structure comprises DNA ends.

6. (original) The method according to claim 4, wherein the damaged DNA comprises UV- irradiated DNA.

7. (original) The method according to claim 1, wherein the test protein comprises a cell extract.

8. (original) The method according to claim 1, wherein the test protein comprises a DNA repair protein.

9. (previously amended) The method according to claim 1, wherein the test protein is detected by contacting the solid support of step (b) with an antibody.

10. (original) The method according to claim 9, wherein said antibody comprises an anti-DNA-PK antibody.

11. (original) The method according to claim 8, wherein the DNA repair protein comprises DNA-PK.

12. (currently amended) A method for measuring an ability of a test substance to modulate a DNA-structure specific binding protein comprising the steps of:

a) Contacting a single DNA substrate comprising a specific structure immobilized on a solid support with a test substance to produce a reaction premix;

b) Contacting the reaction premix of step (a) with a DNA-structure specific binding protein to produce a reaction mix; and

c) Detecting the protein from step (b) while the protein and the DNA substrate ~~is still~~ are bound to the solid support.

13. (canceled) The method of claim 12, wherein the reaction mix is further subjected to a process whereby the DSSBP is detected.

14. (original) The method according to claim 12, wherein the solid support is a microtiter plate.

15. (canceled) The method according to claim 12, wherein the immobilized nucleic acid substrate comprises DNA.

16. (previously amended) The method according to claim 12, wherein the DNA is damaged.

17. (original) The method according to claim 12, wherein the nucleic acid structure comprises DNA ends.

18. (original) The method according to claim 16, wherein the damaged DNA comprises UV- irradiated DNA.

19. (previously amended) The method according to claim 12, wherein the DNA-structure specific binding protein comprises a DNA repair protein.

20. (previously amended) The method according to claim 12, wherein the DNA-structure specific binding protein is detected by contacting the solid support with an antibody.

21. (original) The method according to claim 20, wherein said antibody comprises an anti-DNA-PK antibody.

22. (previously amended) The method according to claim 19, wherein the DNA repair protein comprises DNA-PK.

23. (currently amended) A method for measuring an ability of a test substance to modulate a DNA-structure specific binding protein comprising the steps of:

a) Contacting a DNA-structure specific binding protein with a test substance to produce a reaction premix;
b) Contacting the reaction premix of step (a) with a single DNA substrate comprising a specific structure immobilized on a solid support to produce a reaction mix; and
c) Detecting the protein from step (b) while the protein and DNA substrate ~~is still~~are bound to the solid support.